Clinical trial results:
A Phase 3b Open-label Extension Study Evaluating the Safety of Elexacaftor/Tezacaftor/Ivacaftor Combination Therapy in Cystic Fibrosis Subjects

Summary

EudraCT number	2019-003455-11
Trial protocol	GB DE BE
Global end of trial date	21 December 2022

Results information

Result version number	v1 (current)
This version publication date	06 July 2023
First version publication date	06 July 2023

Trial information

Trial identification

Sponsor protocol code	VX19-445-115

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04362761
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue , Boston, Massachusetts, United States,
Public contact	Medical Information, Vertex Pharmaceuticals Incorporated, +1 617-341-6777, medicalinfo@vrtx.com
Scientific contact	Medical Information, Vertex Pharmaceuticals Incorporated, +1 617-341-6777, medicalinfo@vrtx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2022
Global end of trial reached?	Yes
Global end of trial date	21 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of elexacaftor (VX-445; ELX)/tezacaftor (TEZ)/ivacaftor (IVA)

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 May 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 86
Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	Germany: 36
Country: Number of subjects enrolled	Australia: 30
Worldwide total number of subjects	172
EEA total number of subjects	56

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	51
Adults (18-64 years)	121
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total 172 subjects were enrolled from the parent study VX18-445-109 (NCT04105972). The study was conducted in 2 parts, Part A and Part B.

Period 1

Period 1 title	Part A
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Part A: ELX/TEZ/IVA

Arm description:

Subjects received ELX (elexacaftor) 200 milligram (mg) once daily (qd)/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) in the treatment period for 48 weeks.

Arm type	Experimental
Investigational medicinal product name	Elexacaftor/Tezacaftor/Ivacaftor
Investigational medicinal product code	VX-445/VX-661/VX-770
Other name	ELX/TEZ/IVA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received ELX/TEZ/IVA fixed dose combination once daily in the morning.

Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	IVA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA once daily in the evening.

Number of subjects in period 1	Part A: ELX/TEZ/IVA
Started	172
Completed	159
Not completed	13
Adverse Event	2
Other	5
Withdrawal of consent (not due to AE)	4
Commercial drug is available for subject	2

Period 2

Period 2 title	Part B
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Part B: ELX/TEZ/IVA

Arm description:

Subjects received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the treatment period up to 86 weeks.

Arm type	Experimental
Investigational medicinal product name	Elexacaftor/Tezacaftor/Ivacaftor
Investigational medicinal product code	VX-445/VX-661/VX-770
Other name	ELX/TEZ/IVA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received ELX/TEZ/IVA fixed dose combination once daily in the morning.

Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	IVA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA once daily in the evening.

Number of subjects in period 2[1]	Part B: ELX/TEZ/IVA
Started	50
Completed	0
Not completed	50
Other	4
Commercial drug is available for subject	46

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: A total of 172 subjects were enrolled in the parent study on Part A. However, only 50 subjects rolled over to Part B from Part A of the study.

Baseline characteristics

Reporting groups	
Reporting group title	Part A
Reporting group description:	
Subjects received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 48 weeks.	

Reporting group values	Part A	Total	
Number of subjects	172	172	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	27.9		
standard deviation	± 11.4	-	
Gender categorical Units: Subjects			
Female	87	87	
Male	85	85	
Ethnicity Units: Subjects			
Hispanic or Latino	3	3	
Not Hispanic or Latino	167	167	
Not collected per local regulations	2	2	
Race Units: Subjects			
White	169	169	
Black or African American	0	0	
Asian	2	2	
American Indian or Alaska Native	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Not collected per local regulations	0	0	
White, Asian	1	1	

End points

End points reporting groups

Reporting group title	Part A: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX (elexacaftor) 200 milligram (mg) once daily (qd)/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) in the treatment period for 48 weeks.	
Reporting group title	Part B: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the treatment period up to 86 weeks.	

Primary: Part A: Safety and Tolerability as Assessed by Number of Subjects With Treatment- Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Part A: Safety and Tolerability as Assessed by Number of Subjects With Treatment- Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)[1]
End point description:	
Safety set included all subjects who received at least 1 dose of study drug.	
End point type	Primary
End point timeframe:	
From Day 1 up to Week 52	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were planned. No statistical comparisons were planned for this endpoint.

End point values	Part A: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	172			
Units: Subjects				
Subjects with TEAEs	160			
Subjects with SAEs	26			

Statistical analyses

No statistical analyses for this end point

Primary: Part B: Safety and Tolerability as Assessed by Number of Subjects With Treatment- Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Part B: Safety and Tolerability as Assessed by Number of Subjects With Treatment- Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)[2]
End point description:	
Safety set included all subjects who received at least 1 dose of study drug.	
End point type	Primary

End point timeframe:

From Day 1 up to Week 86

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were planned. No statistical comparisons were planned for this endpoint.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: Subjects				
Subjects with TEAEs	50			
Subjects with SAEs	8			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 up to Week 52 for Part A, Day 1 up to Week 86 for Part B	
Adverse event reporting additional description:	
MedDRA 24.0 applied for Part A and MedDRA 25.1 applied for Part B.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0,25.1

Reporting groups	
Reporting group title	Part A: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg qd in the treatment period for 48 weeks.	
Reporting group title	Part B: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg qd in the treatment period up to 86 weeks.	

Serious adverse events	Part A: ELX/TEZ/IVA	Part B: ELX/TEZ/IVA	
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 172 (15.12%)	8 / 50 (16.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Vascular device occlusion			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Heavy menstrual bleeding			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			
subjects affected / exposed	0 / 172 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dissociative disorder			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 172 (1.16%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			

subjects affected / exposed	2 / 172 (1.16%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forced expiratory volume decreased			
subjects affected / exposed	0 / 172 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb traumatic amputation			
subjects affected / exposed	0 / 172 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus arrest			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Headache			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema nodosum			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			

subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Dupuytren's contracture			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Chronic sinusitis			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	8 / 172 (4.65%)	5 / 50 (10.00%)	
occurrences causally related to treatment / all	1 / 9	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 172 (0.58%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Part A: ELX/TEZ/IVA	Part B: ELX/TEZ/IVA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	127 / 172 (73.84%)	47 / 50 (94.00%)	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	11 / 172 (6.40%)	1 / 50 (2.00%)	
occurrences (all)	12	1	
Aspartate aminotransferase increased			
subjects affected / exposed	11 / 172 (6.40%)	0 / 50 (0.00%)	
occurrences (all)	13	0	
Alanine aminotransferase increased			
subjects affected / exposed	9 / 172 (5.23%)	1 / 50 (2.00%)	
occurrences (all)	18	1	
Injury, poisoning and procedural complications			
Vaccination complication			
subjects affected / exposed	24 / 172 (13.95%)	0 / 50 (0.00%)	
occurrences (all)	36	0	
Procedural pain			
subjects affected / exposed	2 / 172 (1.16%)	3 / 50 (6.00%)	
occurrences (all)	2	3	
Nervous system disorders			
Dizziness			

subjects affected / exposed	11 / 172 (6.40%)	0 / 50 (0.00%)	
occurrences (all)	17	0	
Headache			
subjects affected / exposed	42 / 172 (24.42%)	10 / 50 (20.00%)	
occurrences (all)	73	18	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 172 (4.07%)	8 / 50 (16.00%)	
occurrences (all)	9	8	
Fatigue			
subjects affected / exposed	13 / 172 (7.56%)	1 / 50 (2.00%)	
occurrences (all)	14	1	
Malaise			
subjects affected / exposed	3 / 172 (1.74%)	3 / 50 (6.00%)	
occurrences (all)	4	3	
Immune system disorders			
Immunisation reaction			
subjects affected / exposed	0 / 172 (0.00%)	7 / 50 (14.00%)	
occurrences (all)	0	10	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	12 / 172 (6.98%)	2 / 50 (4.00%)	
occurrences (all)	15	3	
Constipation			
subjects affected / exposed	10 / 172 (5.81%)	4 / 50 (8.00%)	
occurrences (all)	11	5	
Diarrhoea			
subjects affected / exposed	13 / 172 (7.56%)	2 / 50 (4.00%)	
occurrences (all)	27	2	
Gastrooesophageal reflux disease			
subjects affected / exposed	8 / 172 (4.65%)	3 / 50 (6.00%)	
occurrences (all)	20	3	
Abdominal pain			
subjects affected / exposed	16 / 172 (9.30%)	3 / 50 (6.00%)	
occurrences (all)	32	4	
Nausea			

subjects affected / exposed	9 / 172 (5.23%)	1 / 50 (2.00%)	
occurrences (all)	13	1	
Vomiting			
subjects affected / exposed	8 / 172 (4.65%)	3 / 50 (6.00%)	
occurrences (all)	8	3	
Respiratory, thoracic and mediastinal disorders			
Sputum increased			
subjects affected / exposed	19 / 172 (11.05%)	5 / 50 (10.00%)	
occurrences (all)	20	6	
Productive cough			
subjects affected / exposed	4 / 172 (2.33%)	6 / 50 (12.00%)	
occurrences (all)	7	10	
Oropharyngeal pain			
subjects affected / exposed	16 / 172 (9.30%)	5 / 50 (10.00%)	
occurrences (all)	19	7	
Cough			
subjects affected / exposed	23 / 172 (13.37%)	5 / 50 (10.00%)	
occurrences (all)	29	7	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	12 / 172 (6.98%)	2 / 50 (4.00%)	
occurrences (all)	17	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 172 (6.98%)	4 / 50 (8.00%)	
occurrences (all)	15	4	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	17 / 172 (9.88%)	21 / 50 (42.00%)	
occurrences (all)	22	29	
COVID-19			
subjects affected / exposed	2 / 172 (1.16%)	17 / 50 (34.00%)	
occurrences (all)	2	17	
Influenza			

subjects affected / exposed	2 / 172 (1.16%)	3 / 50 (6.00%)	
occurrences (all)	2	3	
Nasopharyngitis			
subjects affected / exposed	28 / 172 (16.28%)	16 / 50 (32.00%)	
occurrences (all)	39	23	
Upper respiratory tract infection			
subjects affected / exposed	10 / 172 (5.81%)	11 / 50 (22.00%)	
occurrences (all)	13	15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 January 2021	Amended to extend treatment period.
19 March 2021	Amended to allow subjects who depart this study to enroll in another qualified Vertex study to return to this study if they did not receive study drug in the Treatment Period of the other qualified Vertex study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported